

### AMENDMENTS TO THE SPECIFICATION

On page 3, please amend the paragraph beginning at line 10 as follows:

In some embodiments, the conjugate is administered as eye drops or as an injection. The compounds of the conjugate include therapeutics for a disease selected from the group consisting of bacterial infections, viral infections, fungal infections, glaucoma, anterior, intermediate, and posterior uveitis, optic neuritis, Leber's neuroretinitis, retinitis, ~~psudotumor/myositis,~~ pseudotumor/myositis, orbital myositis, hemangioma/lymphangioma, toxocariasis, ~~behecet's~~ Behcet's panuveitis, inflammatory ~~chorisretinopathies~~ chorioretinopathies, vasculitis, dry eye syndrome (Sjogren's syndrome), corneal edema, accommodative esotropia, cycloplegia, mydriasis, reverse mydriasis, and macular degeneracy. In some embodiments, the compound is selected from the group consisting of anti-bacterial compounds, anti-viral compounds, anti-fungal compounds, anti-protozoan compounds, anti-histamines, compounds that ~~dialate~~ dilate the pupil, ~~anethstetic~~ anesthetic compounds, steroidal antiinflammatory agents, antiinflammatory analgesics, chemotherapeutic agents, hormones, anticataract agents, neovascularization inhibitors, immunosuppressants, protease inhibitors, aldose reductase inhibitors, corticoid steroids, immunosuppressives, cholinergic agents, anticholinesterase agents, ~~muscarie~~ muscarinic antagonists, sympathomimetic agents,  $\alpha$  and  $\beta$  adrenergic antagonists, and anti-angiogenic factors. Thus, the compounds can include antibacterial compounds, antiviral compounds, cyclosporin, ascomycins and corticosteroids. In some embodiments, the compound is selected from the group consisting of acyclovir and cyclosporins.

On page 10, please amend the paragraph containing line 17 as follows:

"Ocular tissue" refers to tissue of the eye and eyelid. Tissues or layers of the eye include, e.g., the sclera, the cornea, which ~~compries~~ comprises a layer of ~~nonkaratenized~~ nonkeratinized squamous epithelia, the corneal stroma, ~~endotheliuim~~ endothelium, including a cell layer lying on the thick ~~basemnt~~ basement membrane (~~Descemet's~~ Descemet's membrane).

Additional ocular layers include, e.g., ~~The~~ the zona occludens, the aqueous humor, the ~~iris~~ iris, the vitreous ~~humor/vitreous~~ humor/vitreous body, the choroid, the ciliary body including the ciliary epithelium, the retina, including the rod and cone cells, the lens and the optic nerve. *See. e.g., GRAY'S ANATOMY (Williams et al., eds., 1995).*

On page 11, please amend the paragraph containing line 11 as follows:

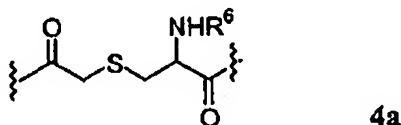
~~“Delivery enhancement” “penetration enhancement”~~ “Delivery enhancement,”  
“penetration enhancement,” or “permeation enhancement” as used herein relates to an increase in amount and/or rate of delivery of a compound that is delivered into and across one or more layers of an epithelial or endothelial tissue or other ocular tissue. An enhancement of delivery can be observed by measuring the rate and/or amount of the compound that passes through one or more layers of such tissue. Delivery enhancement also can involve an increase in the depth into the tissue to which the compound is delivered, and/or the extent of delivery to one or more cell types of the epithelial or other tissue (*e.g.,* increased delivery to cornea, optic nerve, lens or other tissue). Such measurements are readily obtained by, for example, using a diffusion cell apparatus as described in US Patent No. 5,891,462.

On page 13, please amend the paragraph containing line 9 as follows:

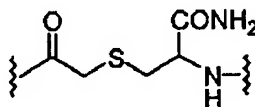
A “subunit,” as used herein, is a monomeric unit that ~~are~~ is joined to form a larger polymeric compound. ~~The set of amino~~ Amino acids are ~~an example~~ examples of subunits. Each amino acid shares a common backbone (-C-C-N-), and the different amino acids differ in their sidechains. The backbone is repeated in a polypeptide. A subunit represents the shortest repeating pattern of elements in a polymer backbone. For example, two amino acids of a peptide are not considered a subunit of a peptide because two amino acids would not have the shortest repeating pattern of elements in the polymer backbone.

On page 28, please amend the paragraph containing lines 22 and 26 as follows:

Linkages of structure 4, are exemplified by formula 4a:



wherein, as above, the wavy lines indicate the point of attachment to each of the transport moiety and the biologically active agent. The preparation of conjugates having linking groups of formula **4a** are shown in Examples 10-12. In Example 10 (see scheme in Figure 32), acyclovir is acylated with  ~~$\alpha$ -chloroacetic~~  $\alpha$ -chloroacetic anhydride to form the  ~~$\alpha$ -chloroacetate~~  $\alpha$ -chloroacetate ester **32i**. Reaction of **32i** with a heptamer of D-arginine having an N-terminal cysteine residue, provides the thioether product **32ii**. Alternatively, acyclovir can be attached to the C-terminus of a transport moiety using a similar linkage formed between acyclovir  ~~$\alpha$ -chloroacetate~~  $\alpha$ -chloroacetate ester and a heptamer of D-arginine having a C-terminal cysteine residue. In this instance, the cysteine residue is provided on the  $r_7$  transport moiety as a C-terminal amide and the linkage has the form:



On page 61, please amend the paragraph containing line 14 as follows:

The nona-peptide, Tat<sub>49-57</sub>, has been previously shown to efficiently translocate through plasma membranes. The goal of this research was to determine the structural basis for this effect and use this information to develop simpler and more effective molecular transporters. Toward this

end, truncated and alanine substituted derivatives of Tat<sub>49-57</sub> conjugated to a ~~fluorescein~~ fluorescein label ~~was~~ were prepared. These derivatives exhibited greatly diminished cellular uptake compared to Tat<sub>49-57</sub>, indicating that all of the cationic residues of Tat<sub>49-57</sub> are required for efficient cellular uptake. When compared with our previous studies on short oligomers of cationic oligomers, these findings suggested that an oligomer of arginine might be superior to Tat<sub>49-57</sub> and certainly more easily and cost effectively prepared. Comparison of short arginine oligomers with Tat<sub>49-57</sub> showed that members of the former were indeed more efficiently taken into cells. This was further quantified for the first time ~~[[bt]]~~ by Michaelis-Menton kinetics analysis which showed that the R9 and r9 oligomers had K<sub>m</sub> values 30-fold and 100-fold greater than that found for Tat<sub>49-57</sub>.

On page 61, please amend the paragraph containing line 30 as follows:

Given the importance of the guanidino head group and the apparent insensitivity of the oligomer chirality revealed in our peptide studies, we designed and synthesized a novel series of polyguanidine peptoids. The peptoids *N*-arg<sub>5,7,9</sub>, incorporating the arginine side chain, exhibited comparable cellular uptake to the corresponding *d*-arginine peptides r<sub>5,7,9</sub>, indicating that the hydrogen bonding along the peptide backbone and backbone chirality are not essential for cellular uptake. This observation is consistent with molecular models of these peptoids, arginine oligomers, and Tat<sub>49-57</sub>, all of which have a deeply embedded backbone and a guanidinium dominated surface. Molecular models further reveal that these structural characteristics are retained in varying degree in oligomers with different alkyl spacers between the peptoid backbone and guanidino head groups. Accordingly, a series of peptoids incorporating 2- (*N*-etg), 4- (*N*-btg), and 6-atom (*N*-hxg) spacers between the backbone and side chain were prepared and compared for cellular uptake with the *N*-arg peptoids (3-atom spacers) and *d*-arginine oligomers. The length of the side chains had a dramatic ~~effect~~ effect on cellular entry. The amount of cellular uptake was proportional to the length of the side chain with *N*-hxg > *N*-btg > *N*-arg > *N*-etg. Cellular uptake was improved when the number of alkyl spacer units between the guanidine head group and the backbone was increased. Significantly, *N*-hxg<sub>9</sub> was superior to r<sub>9</sub>, the latter being 100-fold better than Tat<sub>49-57</sub>. This result

led us to prepare peptoid derivatives containing longer octyl spacers (*N*-ocg) between the guanidino groups and the backbone. Issues related to solubility prevented us from testing these compounds.